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(54) Title: OPHTHALMIC COMPOSITIONS BASED ON POLYHYDRIC ALCOHOLS

(57) Abstract

The present invention relates to an ophthalmic composition comprising at least one active principle and at least one ophthalmically acceptable osmotic agent having antimicrobial activity, typically xylitol; and to a process for the preparation thereof.

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OPHTHALMIC COMPOSITIONS BASED ON POLYHYDRIC ALCOHOLS

The present invention relates to ophthalmic compositions, and concerns more especially the preservatives contained in ophthalmic compositions.

Ophthalmic compositions generally consist of at least one active principle, and an excipient containing at least one inorganic or organic osmotic agent which imparts to the preparation an osmotic pressure corresponding to that of the lachrymal fluid. The osmotic pressure of the lachrymal fluid is equivalent to that of a 0.93% NaCl solution.

An inorganic osmotic agent commonly employed in ophthalmic preparations is sodium chloride. Examples of organic osmotic agents commonly employed in ophthalmic formulations include hydrogenated hexoses such as mannitol and sorbitol.

Ophthalmic compositions must also be sterile when used. However, whilst sodium chloride remains neutral with respect to bacterial growth, the hydrogenated hexoses generally employed as excipients tend to promote microorganism growth.

It is hence necessary either to prepare sterile single doses which are discarded after each use, thereby increasing production costs, or to incorporate into the ophthalmic composition preservatives which are microorganism growth inhibitors.

The preservatives generally employed have many drawbacks. In particular, they might exhibit some degree of toxicity through the corneal epithelium, or else they might induce allergic reactions if used at excessively high concentrations. Alternatively, if used at too low

concentrations, certain preservatives may not be sufficiently active against some microorganisms.

We have now found unexpectedly that certain acceptable osmotic agents, namely those having antimicrobial activity, may advantageously replace, partially or wholly, the osmotic agents commonly used in ophthalmic compositions, thereby enabling the use of possibly toxic or irritant preservatives to be decreased or even excluded and the spectrum of microorganisms eliminated to be broadened. A class of acceptable osmotic agents of particular value in this regard includes the hydrogenated pentose derivatives such as xylitol and related compounds of the xylitol type.

The present invention accordingly relates to an ophthalmic composition comprising at least one active principle and an excipient, characterised in that the excipient contains at least one ophthalmically acceptable osmotic agent having antimicrobial activity, preferably a hydrogenated pentose derivative such as xylitol.

By the expression "ophthalmically acceptable osmotic agent" is meant a compound which imparts to an ophthalmic composition an osmotic pressure corresponding to that of a NaCl solution which is acceptable to the eye; in other words, a composition which neither irritates nor adversly affects the parts of the eye with which it will come into contact. By way of guidance, it is to be noted that the limits imposed by the USP for acceptable ophthalmic solutions are from 0.6 to 2% by weight of NaCl.

The hydrogenated pentose derivatives, such as xylitol or related compounds of the xylitol type, may be employed alone or mixed with at least one other osmotic agent suitably selected from sodium chloride, mannitol, sorbitol and mixtures thereof.

By the expression "agent having antimicrobial activity" is meant a compound which inhibits microorganism growth or destroys microorganisms, such microorganisms typically including bacteria and fungi.

The composition according to the invention may also advantageously incorporate at least one standard preservative. Examples of suitable preservatives include benzalkonium chloride, thimerosal, benzododecinium bromide, parabens and their sodium salts, chlorobutanol, aromatic alcohols, chlorhexidine, and mercury derivatives, as well as other preservatives well known to those skilled in the art, and mixtures thereof.

The ophthalmic composition according to the present invention may suitably take the form of a solution, a gel, a suspension or an emulsion, preferably an aqueous solution. The ophthalmically acceptable osmotic agent having antimicrobial activity such as a hydrogenated pentose derivative, e.g. xylitol, is employed therein as a replacement for the osmotic agents commonly used in known preparations of the prior art.

The ophthalmically acceptable osmotic agent having antimicrobial activity is incorporated into the preparations of the present invention such that these preparations display a cryoscopic lowering property of between -0.34°C and -1.16°C. An ophthalmic composition in accordance with the present invention capable of showing such a cryoscopic lowering typically comprises from 0.1 to 9%, preferably from 2.0 to 9%, by weight of xylitol.

It is possible to use in the composition according to the invention a wide variety of active principles. They may typically be selected from the following pharmaceutical compounds:

- antibacterial substances such as beta-lactam antibiotics, for example cefoxitin, n-formamidoylthienamycin and other thienamycin derivatives, tetracyclines, chloramphenicol, neomycin, carbenicillin, colistin, penicillin G, polymyxin B, vancomycin, cefazolin, cephaloridine, chibrorifamycin, gramicidin, bacitracin and sulfonamides;
aminoglycoside antibiotics such as gentamycin, kanamycin, amikacin, sisomicin and tobramycin;
nalidixic acid and its analogues such as norfloxacin and the antimicrobial combination fluoroalanine/pentizidone, nitrofurazones and analogues thereof;
- antihistamines and decongestants such as pyrilamine, chlorpheniramine, tetrahydrazoline, antazoline and analogues thereof;
- anti-inflammatories such as cortisone, hydrocortisone, hydrocortisone acetate, betamethasone, dexamethasone, dexamethasone sodium phosphate, prednisone, methylprednisolone, medrysone, fluorometholone, prednisolone, prednisolone sodium phosphate, triamcinolone, indomethacin, sulindac, its salts and corresponding sulphides, and analogues thereof;
- miotics and anticholinergics such as echothiopate, pilocarpine, physostigmine salicylate, diisopropyl-fluorophosphate, epinephrine, dipivaloylepinephrine, neostigmine, echothiopate iodide, demecarium bromide, carbamoyl choline chloride, methacholine, bethanechol and analogues thereof;
- mydriatics such as atropine, homatropine, scopolamine, hydroxyamphetamine, ephedrine, cocaine, tropicamide, phenylephrine, cyclopentolate, oxyphenonium, eucatropine and analogues thereof;
- other drugs used in the treatment of eye conditions and lesions, such as antiglaucoma drugs, for example timolol,

R-timolol, and a combination of timolol or R-timolol with pilocarpine, as well as many other adrenergic agonists and/or antagonists; epinephrine, and epinephrine complexes or prodrugs, and dipivefrine derivatives and hyperosmotic agents such as glycerol, mannitol and urea; and carbonic anhydrase inhibitors such as acetazolamide, dichlorphenamide, 2-(p-hydroxyphenyl)thio-5-thiophenesulphonamide, 6-pivaloyloxy-2-benzothiazolesulphonamide, MK-927 and MK-417;

- antiparasitic compounds and/or antiprotozoal compounds such as ivermectin, pyrimethamine, trisulphapyrimidine, clindamycin and corticosteroid preparations;

- compounds having antiviral activity such as acyclovir, 5-iodo-2'-deoxyuridine (IDU), adenosine arabinoside (Ara-A), trifluorothymidine, and interferon and interferon-inducing agents such as polyI.polyC;

- antifungal agents such as amphotericin B, nystatin, flucytosine, natamycin and miconazole;

- anaesthetic agents such as etidocaine, cocaine, benoxinate, dibucaine hydrochloride, dyclonine hydrochloride, naepaine, phenacaine hydrochloride, piperocaine, proparacaine hydrochloride, tetracaine hydrochloride, hexylcaine, bupivacaine, lidocaine, mepivacaine and prilocaine;

- ophthalmic diagnostic agents such as:

a) those which are used for examining the retina, such as fluorescein sodium;

b) those which are used for examining the conjunctiva, cornea and lachrymal apparatus, such as fluorescein and rose bengal; and

c) those which are used for examining abnormal responses of the pupil, such as methacholine, cocaine, adrenaline, atropine, hydroxyamphetamine and pilocarpine;

- ophthalmic agents used as surgical aids, such as alpha-chymotrypsin and hyaluronidase;
- chelating agents such as ethylenediaminetetraacetic acid (ETDA) and deferoxamine;
- immunosuppressants and antimetabolites such as methotrexate, cyclophosphamide, 6-mercaptopurine and azathioprine; and antibiotic/anti-inflammatory combinations such as the combination neomycin sulphate/dexamethasone sodium phosphate, and combinations concomitantly treating glaucoma, for example a timolol maleate/aceclidine combination.

The active principle may typically be present in the ophthalmic composition according to the invention in an amount of from about 0.001% to about 5% by weight, suitably from 0.1% to 2% by weight.

Finally, gelling or viscosifying agents may be advantageously incorporated into the preparations of the present invention. Such agents include in particular polysaccharides such as gellan gum, especially the product sold by the Kelco company under the trade name Gelrite; carboxylic polymers such as those designated by the trade mark Carbopol; cellulose derivatives, for example carboxymethylcellulose or hydroxyethylcellulose (HEC); polyvinyl alcohols (PVA); polyvinylpyrrolidone (PVP); and mixtures thereof.

It will be appreciated that, in practice, certain gelling or viscosifying agents have a tendency to be incompatible with certain mineral osmotic agents. For example, Gelrite^{R} interacts rapidly with sodium chloride to form a gel, and Carbopol^{R} gives an unwanted precipitate in the presence of sodium chloride. Combinations of gelling or viscosifying agents and mineral osmotic agents which interact undesirably in this way are consequently best avoided. The person skilled in

the art will either be already aware of which combinations to avoid, or be capable of ascertaining such incompatible combinations on the basis of simple trial and error.

The present invention also concerns a process for preparing the above-described composition, characterised in that an ophthalmically acceptable osmotic agent having antimicrobial activity is mixed with the other components constituting the composition under agitation in an aqueous solution and then sterilized.

Table I below describes the composition of two dilute ophthalmic solutions, one being rendered isotonic with xylitol according to the present invention (Example 1), the other being rendered isotonic in a conventional manner with mannitol (Example 2). The proportions are given in percentages by weight relative to the total weight of the composition.

Both solutions are prepared in an identical way by dissolving the different compounds in water under agitation, the gelling or viscosifying agent being incorporated last. After dissolving all the components, the ophthalmic solutions are sterilized in an autoclave.

Both compositions have an identical concentration of preservative (0.01% benzododecinium bromide), and differ only in the tonicity agent employed.

TABLE 1

	EXAMPLE 1	EXAMPLE 2
Timolol maleate	0.684	0.684
Xylitol	3.20	0
Mannitol	0	4.05
Trometharnine	0.182	0.182
Benzododecinium bromide, anhydrous	0.01	0.01
Gelrite^{R}, anhydrous	0.60	0.60
Water for injection qs	100	
Freezing-point depression	-0.51°C	-0.54°C

A simplified test of efficacy of preservatives according to the British Pharmacopoeia (1988, Appendix XVI C) was performed for the two compositions, with respect to Aspergillus niger.

The results of these comparative tests, as displayed in Table II below, show clearly the major advantage of incorporating xylitol into a composition of this type.

TABLE II

Aspergillus niger count according to the B.P., 1988

	EXAMPLE 1	EXAMPLE 2
Inoculum	9.00×10^{6}	1.80×10^{7}
Time zero	8.00×10^{4}	1.60×10^{5}
7 Days	40	6.50×10^{3}
14 Days	1	6.00×10^{3}

CLAIMS:

1. An ophthalmic composition comprising at least one active principle and an excipient, characterised in that the excipient contains at least one ophthalmically acceptable osmotic agent having antimicrobial activity.

2. A composition as claimed in claim 1, characterised in that the ophthalmically acceptable osmotic agent having antimicrobial activity is a hydrogenated pentose derivative.

3. A composition as claimed in claim 2, characterised in that the ophthalmically acceptable osmotic agent having antimicrobial activity is xylitol.

4. A composition as claimed in any one of the preceding claims, characterised in that it further contains at least one other osmotic agent selected from sodium chloride, mannitol, sorbitol and mixtures thereof.

5. A composition as claimed in any one of the preceding claims, characterised in that it further contains at least one standard preservative.

6. A composition as claimed in any one of the preceding claims, characterised in that it comprises from 0.1 to 9% by weight of xylitol.

7. A composition as claimed in any one of the preceding claims, characterised in that it further comprises a gelling or viscosifying agent.

8. A composition as claimed in claim 7, characterised in that the gelling or viscosifying agent is selected from polysaccharides, carboxylic polymers, cellulose derivatives, and mixtures thereof.

9. A composition as claimed in any one of the preceding claims, characterised in that the active principle is selected from antiglaucoma drugs, antibiotics and compounds having antiviral activity.

10. A process for preparing an ophthalmic composition as claimed in any one of the preceding claims, characterised in that an ophthalmically acceptable osmotic agent having antimicrobial activity is mixed with the other components constituting the composition under agitation in an aqueous solution and then sterilized.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01407

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/08 A 61 K 47/26 A 61 K 31/70

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	GB,A,2199745 (HOKURIKU) 20 July 1988, see claims; page 3, lines 18-20,30; page 4, lines 15-24	1,3,5-6 ,9-10
X	Database: WPIL, accession no. 88-016591 (03), Derwent Publications Ltd, London, GB, & JP,A,62277323 (SANKYO K.K.) 2 December 1987, see abstract	1-3,5-6 ,9-10
X	EP,A,0080879 (SUNSTAR) 8 June 1983, see claims 1-2,12; page 2, lines 10-15; page 3, lines 15-19; page 6, lines 6-9,15	1-4,7-10

° Special categories of cited documents :[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16-10-1992	20. 11. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201407 SA 63139

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 06/11/92
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 2199745	20-07-88	JP-A- 63174930	19-07-88
		CH-A- 676549	15-02-91
		DE-A,C 3715918	28-07-88
		FR-A- 2609394	15-07-88
		SE-A- 8701961	15-07-88
		US-A- 4780465	25-10-88
EP-A- 0080879	08-06-83	JP-A- 58167520	03-10-83
		JP-C- 1452214	25-07-88
		JP-A- 58092619	02-06-83
		JP-B- 62060370	16-12-87
		JP-B- 3008323	05-02-91
		JP-A- 58092620	02-06-83
		JP-A- 58092621	02-06-83
		JP-A- 58092622	02-06-83
		US-A- 4675184	23-06-87